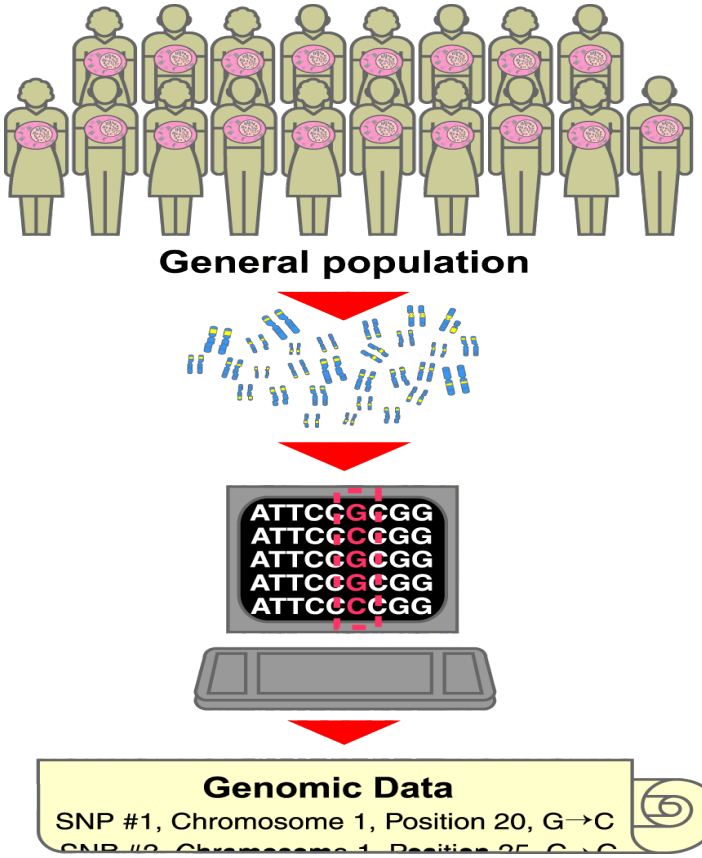
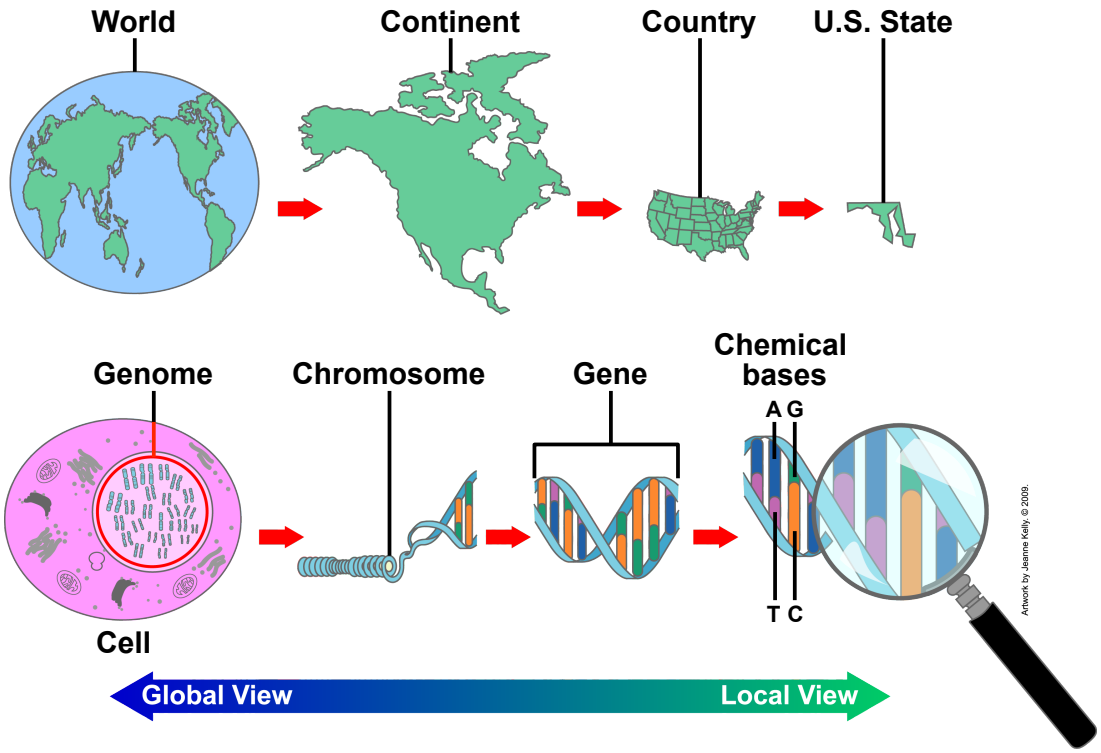
# Understanding Genome-Wide Profiling of Cancer




*Donna Kerrigan, M.S.*
*E. Milliken, Ph.D.*
*L.M. Bennett, Ph.D.*

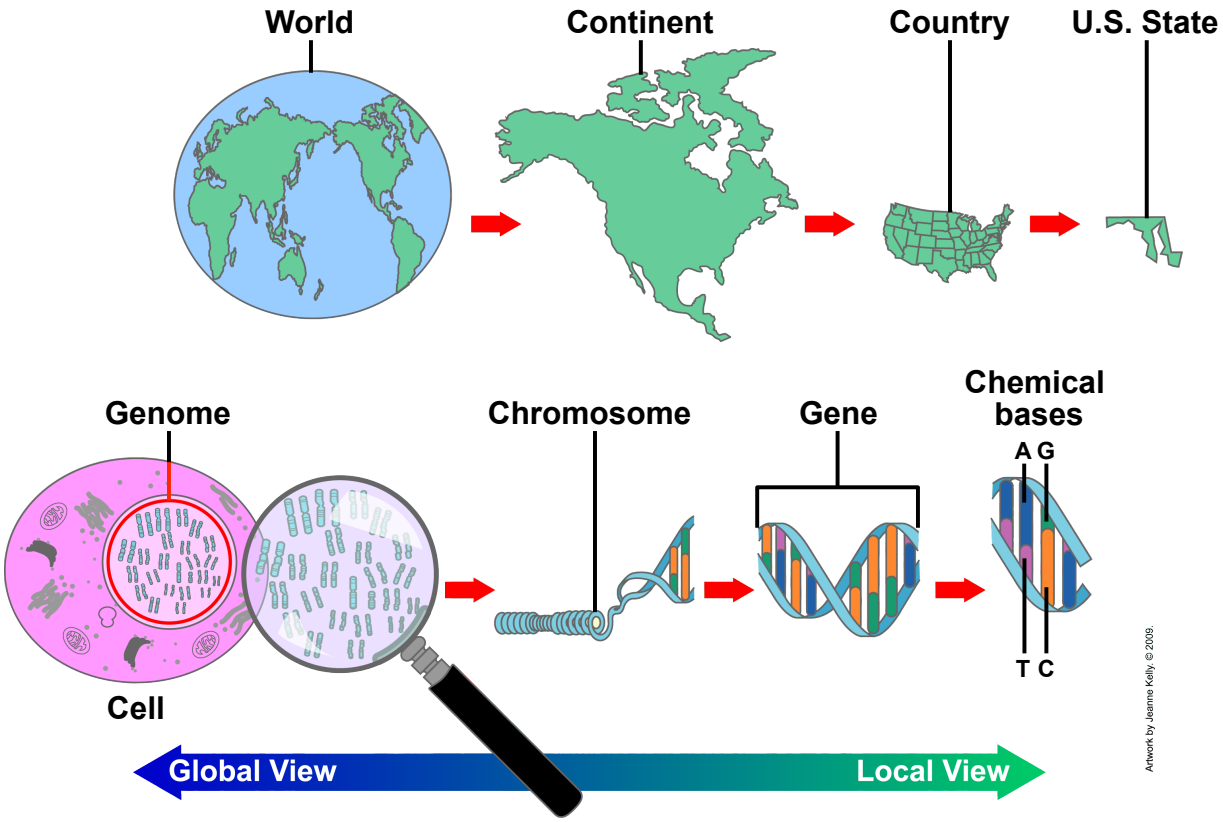
# Single Gene Tests:
# A Locally Focused Search




Single-gene tests focus on a specific, known location in a patient's genome. Using this approach, scientists have looked for single genes linked to cancer. This research has revealed some important discoveries such as gene changes called mutations located within the BRCA1 or BRCA2 genes that may confer a significantly increased risk of breast and ovarian cancer. And some single-gene tests continue to inform treatment decisions. For example, colon cancer patients may be tested for a K-ras mutation, or breast cancer patients for HER2 gene activity, before treatment is planned.

A geographical analogy helps depict the scale of the search involved in single-gene tests.

# Genome-Wide Profiling:
# A Globally Focused Search

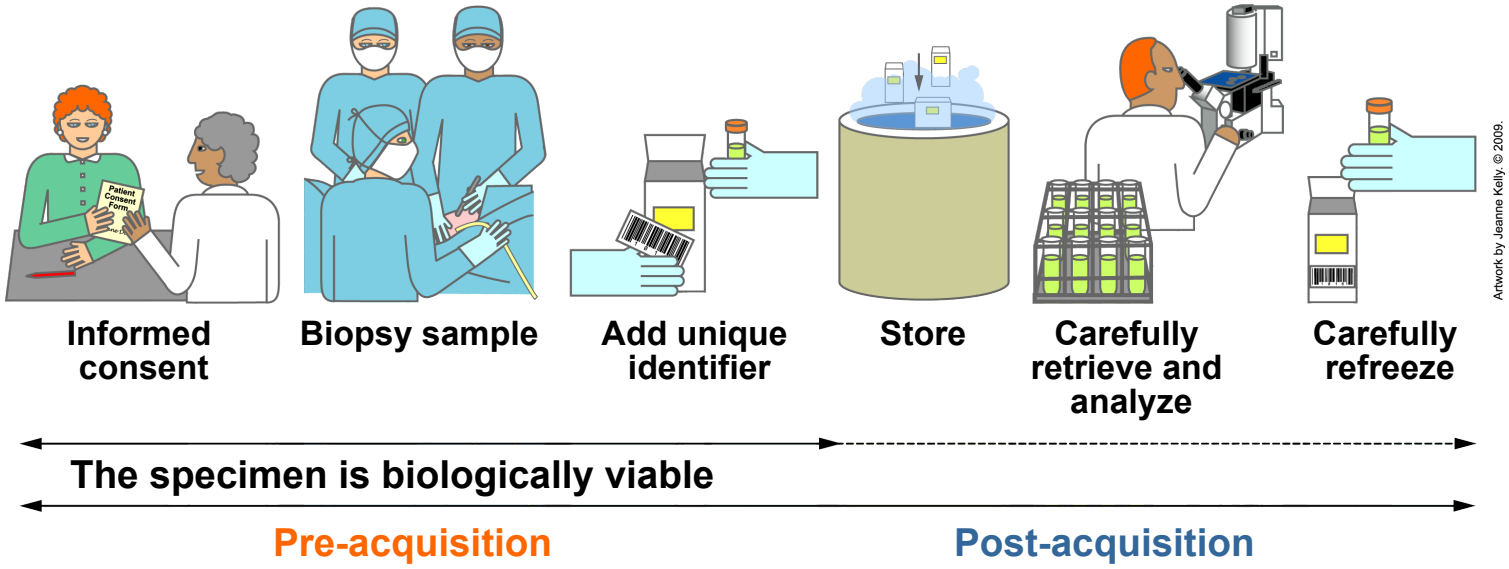



But single-gene tests *alone* are unable to completely unravel the complexity of cancer. They very rarely explain why cancer has developed. Because cancer involves the simultaneous interaction of many different mutated genes and proteins within malignant cells and their surrounding normal tissues, a global approach is needed to capture all the activity. Scientists have developed new methods to cast a genome-wide search and look globally for all the changes in DNA, RNA, or proteins* that contribute to cancer's existence. These new approaches are collectively called genome-wide profiling.

Again, a geographical analogy shows the global scale of the search involved in genome-wide profiling.

*To learn more basic information about DNA, RNA, and proteins in relation to the molecular diagnosis of cancer, please visit **http://www.nci.nih.gov/cancertopics/understandingcancer/moleculardiagnostics/**

# Starts with
# Proper Collection and Storage




Genome-wide profiling requires proper sample collection and storage. This is why biopsy specimens must be collected, stored, tracked, and used according to the highest scientific and ethical standards.

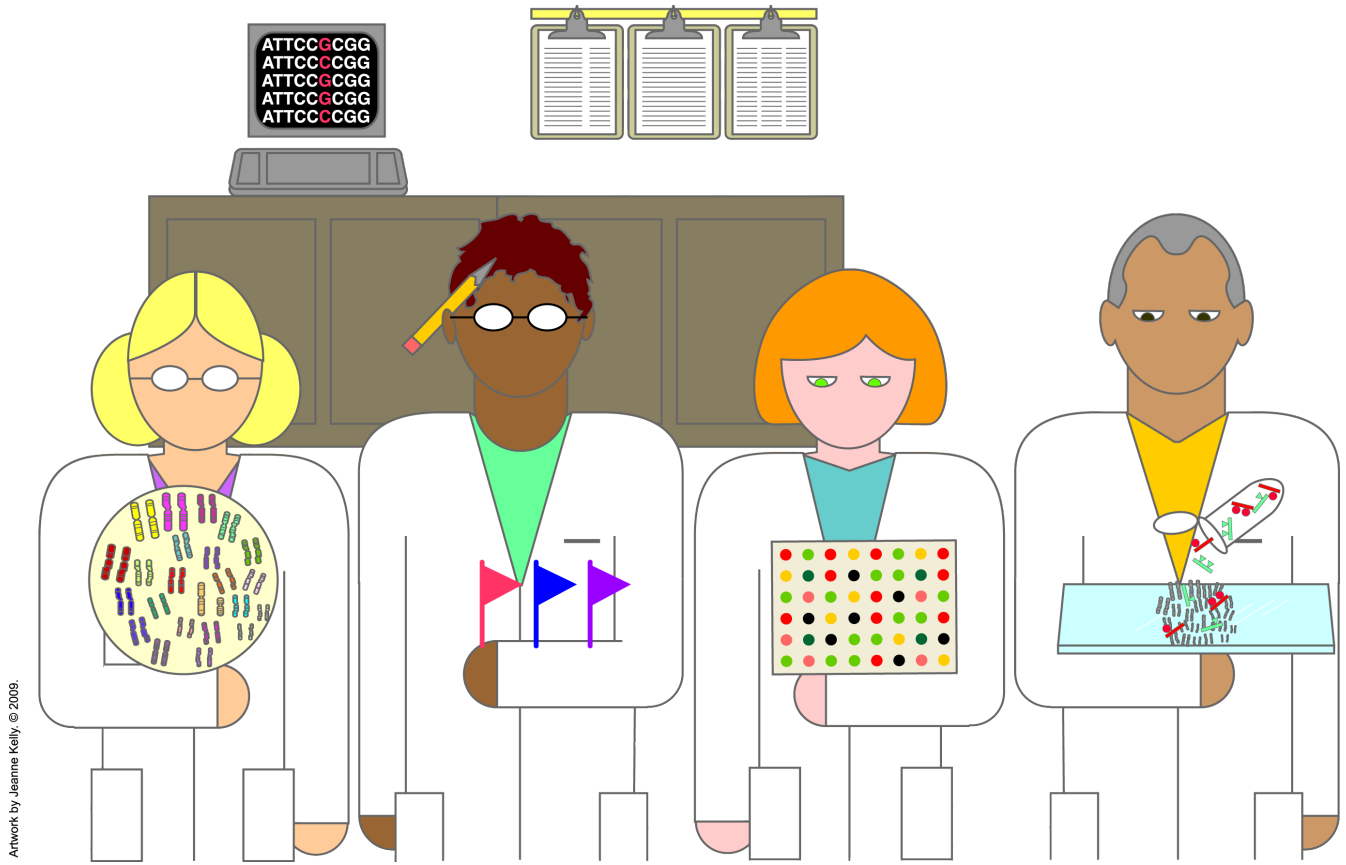
Informed consent for use of cancerous biopsy specimens (or a waiver of this consent) must be in place at the time of collection.

Samples must be given an electronic, unique identifier that links the specimen to a patient, to a treatment protocol, and to the informed consent (or waiver).

Samples must be stored and retrieved following best clinical practices.

When all this is in order, a researcher can use the biopsy sample to get a genome-wide profile of the cancer.

# Genome-Wide Profiling: Many Ways




Genome-wide profiling refers to the collection of large-scale information about the sequence and expression of the genes in normal or tumor cells. Techniques include:

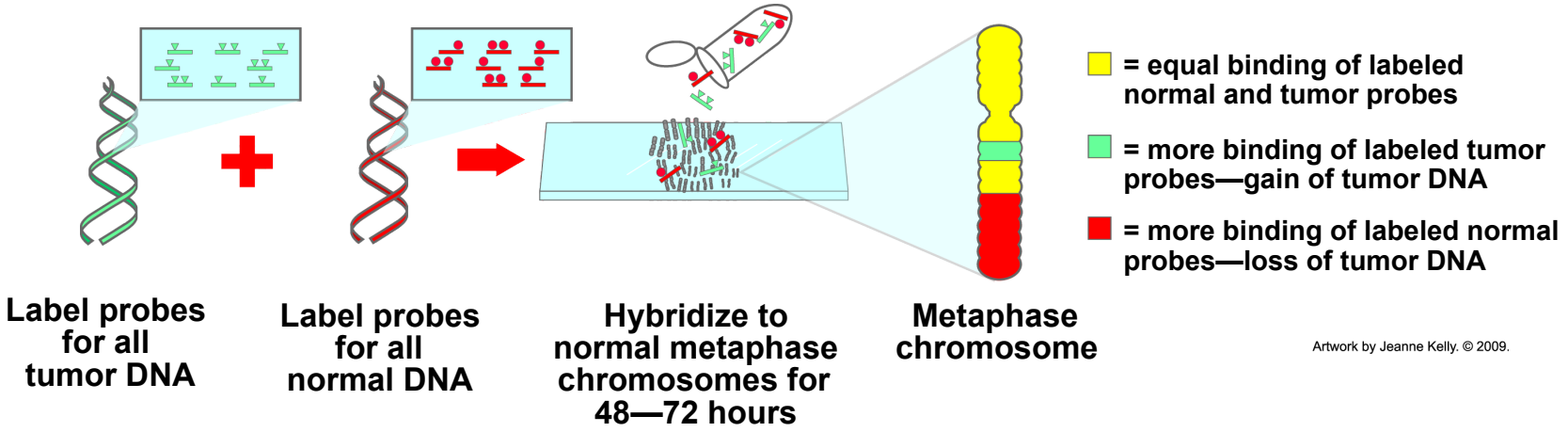
• *Comparative Genomic Hybridization and Spectral Karyotyping*
looking at global changes in chromosome structure when cancer cells are compared to normal tissues from the same patient

• *Polymorphism Analysis*
looking at sets of genetic variations called polymorphisms in individuals and in populations (These specific altered regions or sequences are spread across the entire genome.)

• *Gene Expression Profiling*
capturing total gene activities, both increases and decreases, across a genome as patterns of gene expression

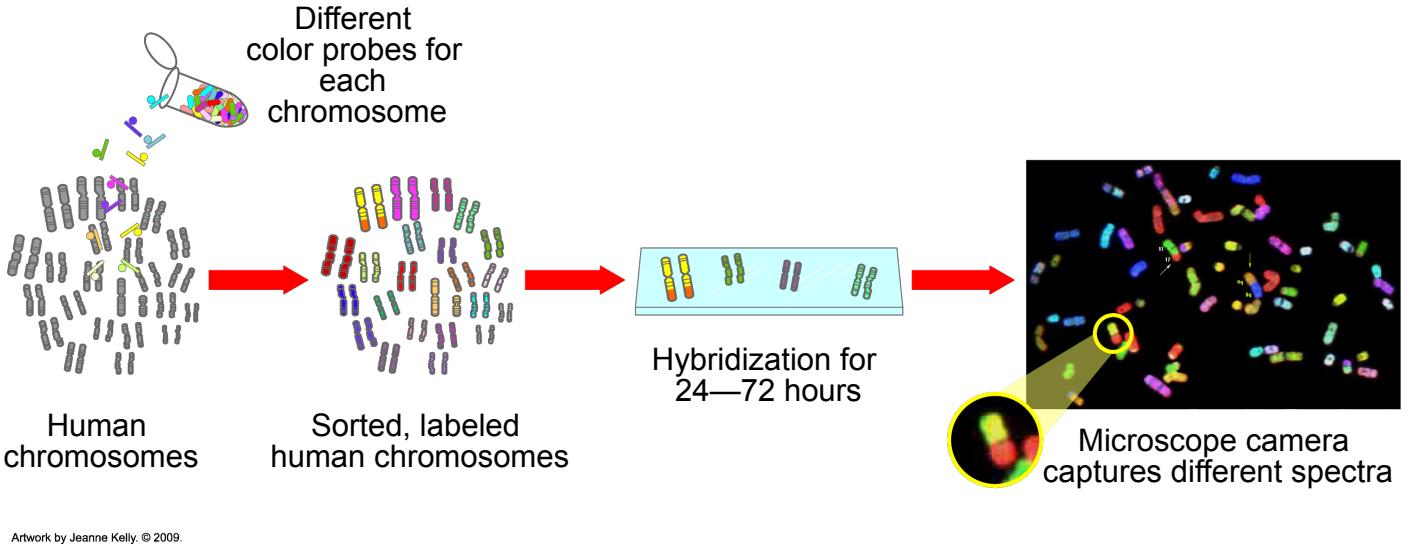
Most of these techniques use high-throughput technologies, which are automated systems that can perform rapid analysis of large numbers of samples in a short period of time. Genomic signatures or genomic profiles that are validated can be used to identify a specific tumor type in new tissue samples.

# Genome-Wide Profiling: Comparative Genomic Hybridization




Comparative genomic hybridization (CGH) is a method that allows researchers to detect large-scale changes in chromosomes. They can visualize where extra genetic material (repeating copies) has been added or deleted. They can see where large portions of genetic material have been inserted into chromosomes. Many cancers exhibit these types of chromosomal abnormalities.

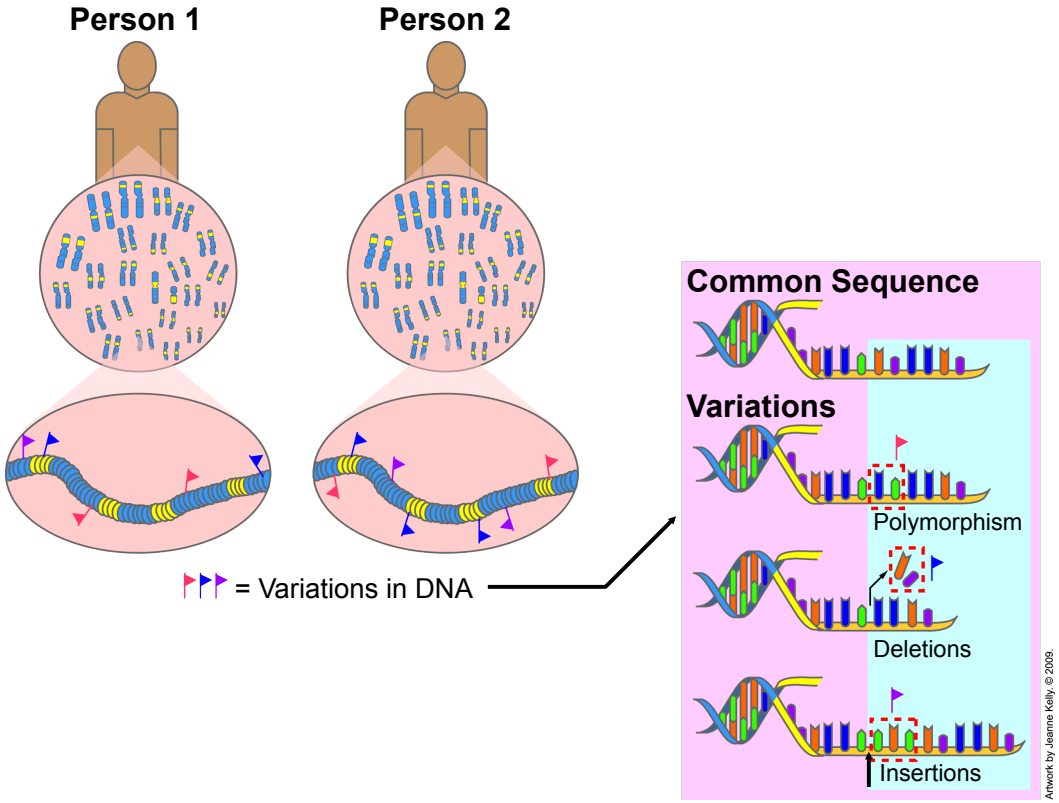
# Genome-Wide Profiling: Karyotyping





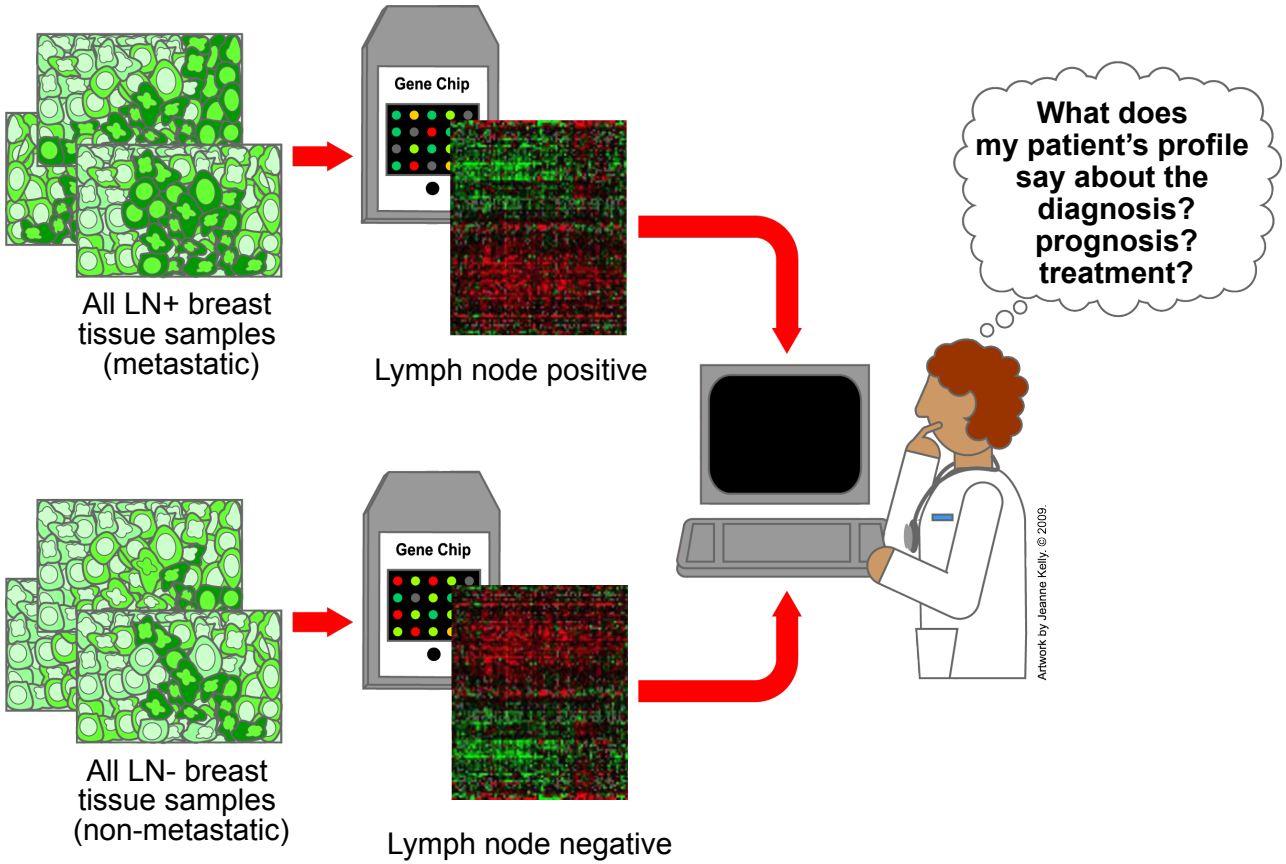

Spectral karyotyping is a method that allows researchers to visualize each chromosome using a different color. This technology is powerful because it makes it possible to see where genetic material has been added or exchanged within a cancer genome.

# Genome-Wide Profiling: Polymorphism Analysis



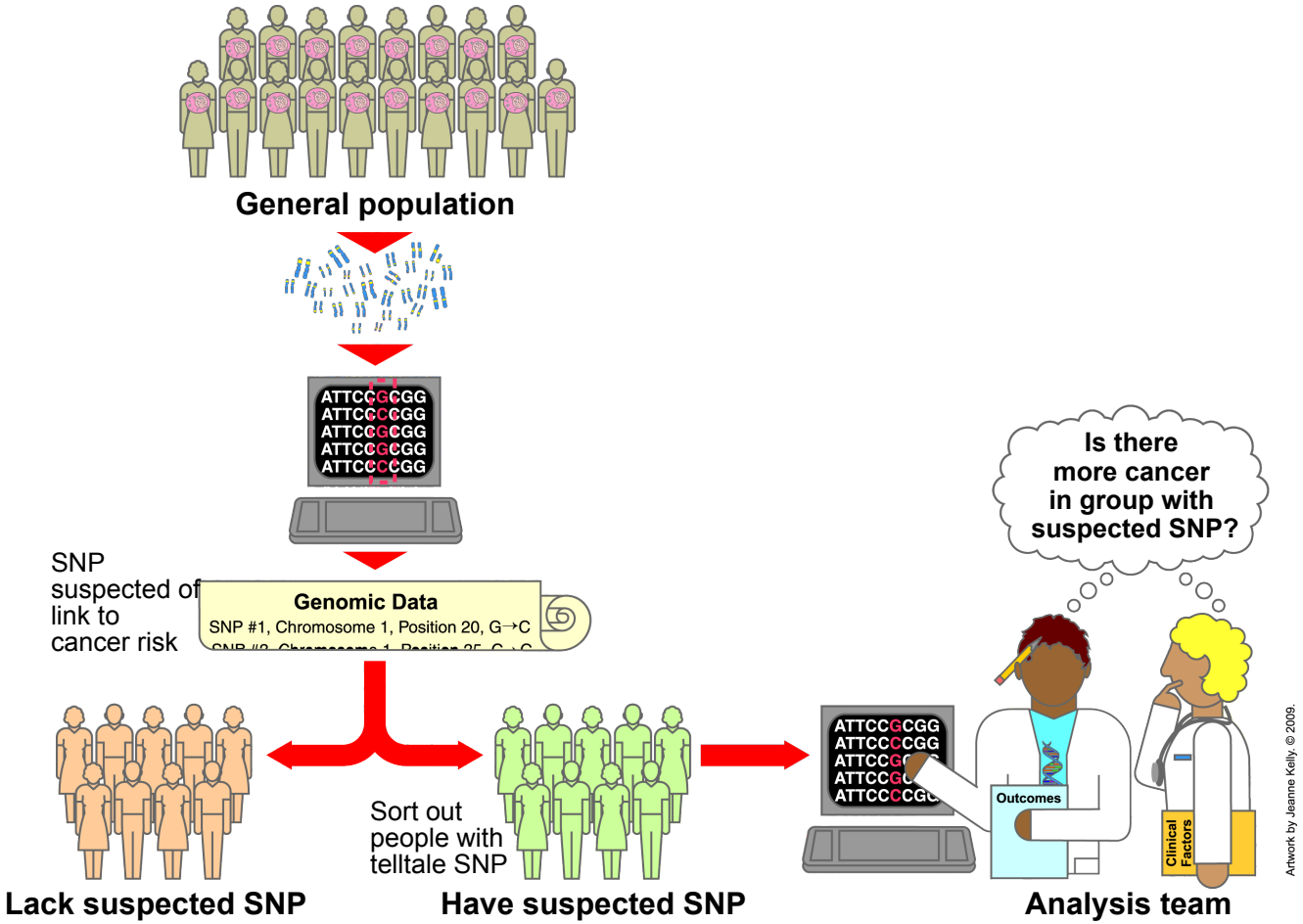

Another approach is called polymorphism analysis. Polymorphism analysis is used to find variation in genetic sequence across the genome; some tests look for sets of telltale variations in single base pairs (single-nucleotide polymorphisms), whereas others look for tandem repeats (simple sequence repeats) or insertions of several telltale bases (restriction-fragment length polymorphisms). Once sequence polymorphisms that are potentially associated with cancer are identified, these must be validated through further research in independent populations. Polymorphism data will be used in conjunction with other genetic, genomic, and clinical information.

# Genome-Wide Profiling: Gene Expression Profiles




Researchers use gene expression profiling to study the activity of genes in a patient's tumor sample and compare it to normal tissue of the same type. This approach measures levels of messenger RNA (mRNA), which is a good indicator of the proteins about to be made by the cell. An individual's messenger RNA is processed and labeled and then applied to a specially designed chip, often referred to as a microarray, which includes complementary sequences for hundreds of thousands of genes. A chip reader measures levels of the expressed genes in the sample.

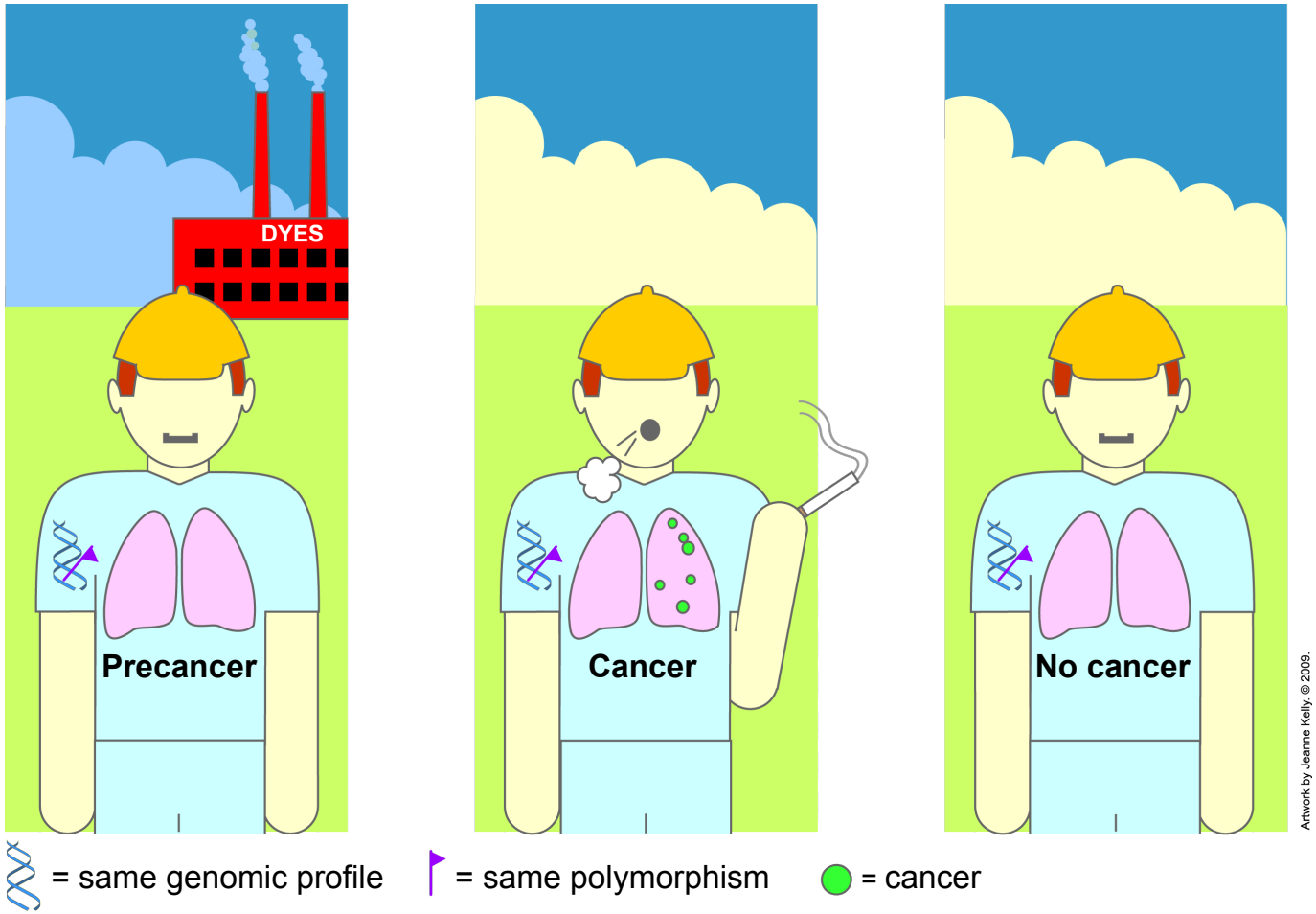
# Why Is It Important To Collect Genome-Wide Profiles?




Genomic profiling provides a way to collect extensive information about individuals, analyze the profiles from many patients and their tumor(s), and use databases and analytical tools (informatics) to discover important differences. Researchers hope to correlate genomic profiles with known clinical factors and outcomes.

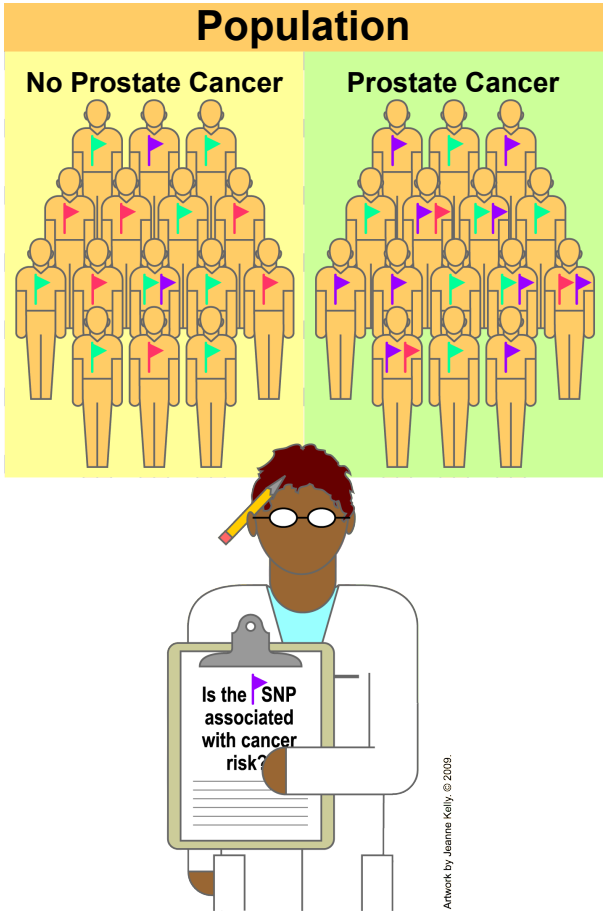
# Can Genome-Wide Profiles Predict Cancer Risk?

## Same profile, different environment = different result




Not yet. Cancer is a complex disease that is driven by genetic, lifestyle, and environmental factors. Furthermore, each individual and each tumor are unique. Thus, it has proven difficult to identify a predictive genomic profile that is valid for multiple populations. Claims that a particular genomic profile can predict cancer risk should be interpreted with caution. It is likely that genomic profiles will need to be used in conjunction with other genetic and clinical information to accurately assess a person's cancer risk.

# Can Genome-Wide Profiling Discover Polymorphisms That May Influence Cancer Risk?

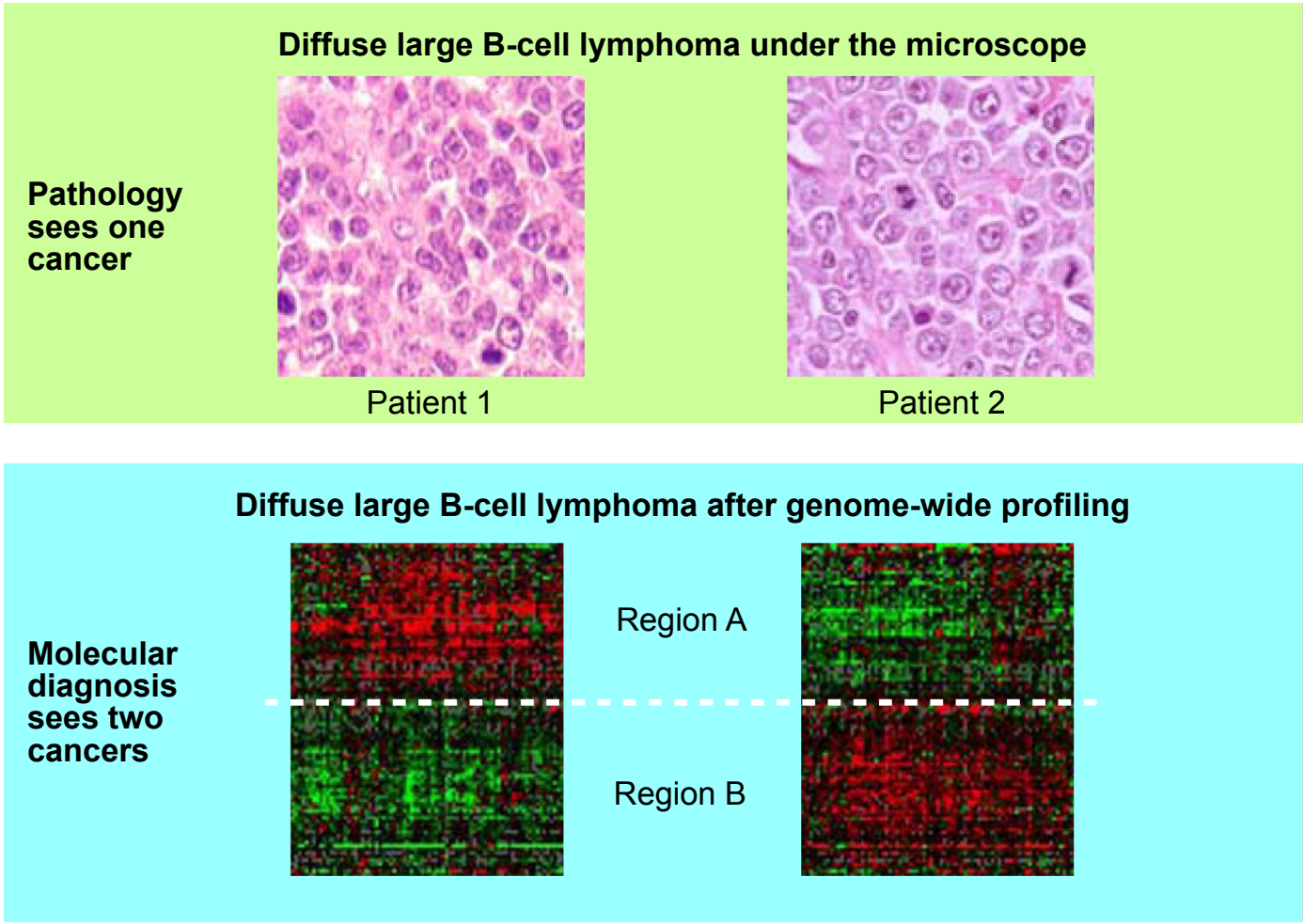



Possibly. Studies of polymorphisms in individual patients and in populations are yielding interesting hints. Some (but not all) sequence polymorphisms appear to influence cancer risk. Some sequence polymorphisms may not themselves be associated with cancer risk but may serve as "markers" for nearby genes that *do* exert an influence.

Polymorphisms within protein coding regions may alter the function of the encoded protein, particularly if they change its structure or amino acid sequence. Polymorphisms in regions of the DNA that regulate gene expression may result in altered protein levels, alternative splicing, or other modifications.

Changes in a protein's sequence or its regulation can influence cancer risk by altering how a person responds to carcinogens, drugs, chemicals, or other environmental exposures.

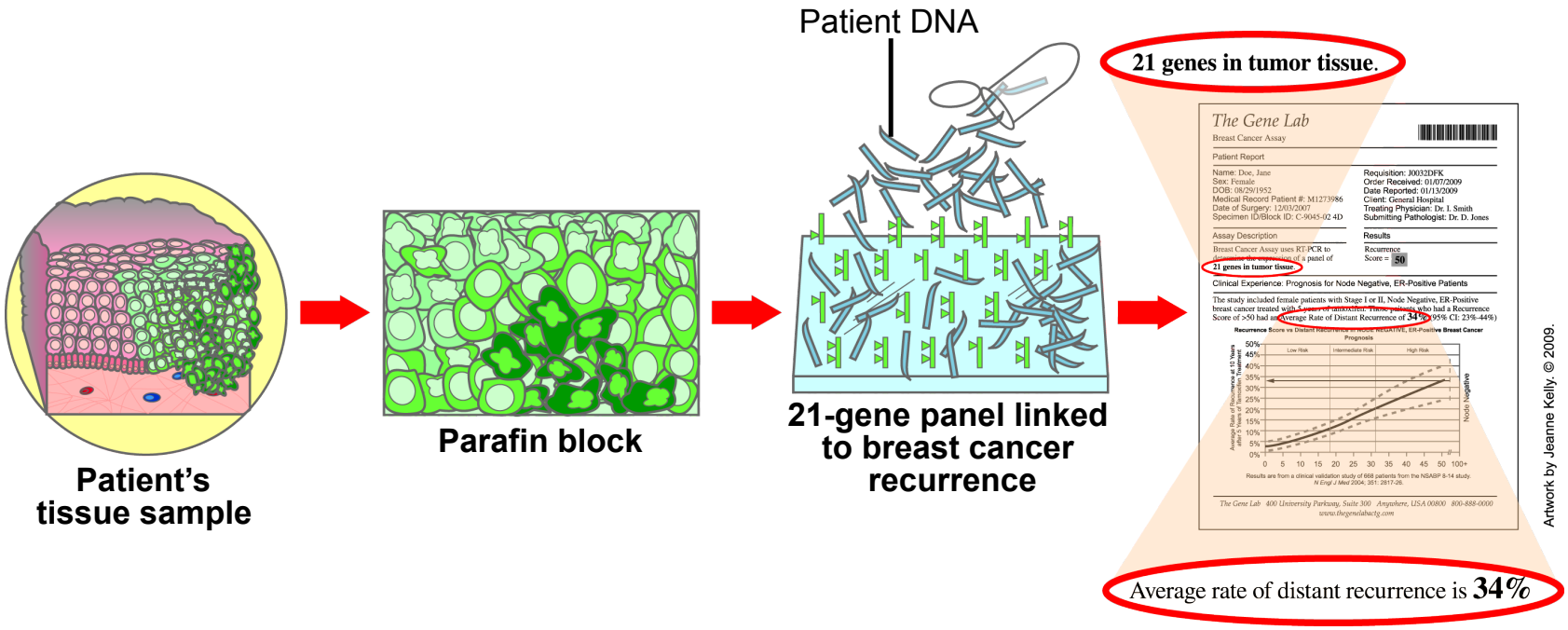
# Can Genome-Wide Profiles Help Diagnose Cancer?




Yes. Genomic profiles can be used to subclassify certain cancers within pathologically defined groups. These profiles can further differentiate tumors that look similar under the microscope. Gene expression microarrays—the major tool used to measure the genome-wide changes in gene expression—have been used experimentally to subclassify acute myelogenous leukemias and to distinguish Burkitt's from diffuse large B-cell lymphoma. And work is under way to build a genome-based classification system for glioma, the most common type of brain tumor.

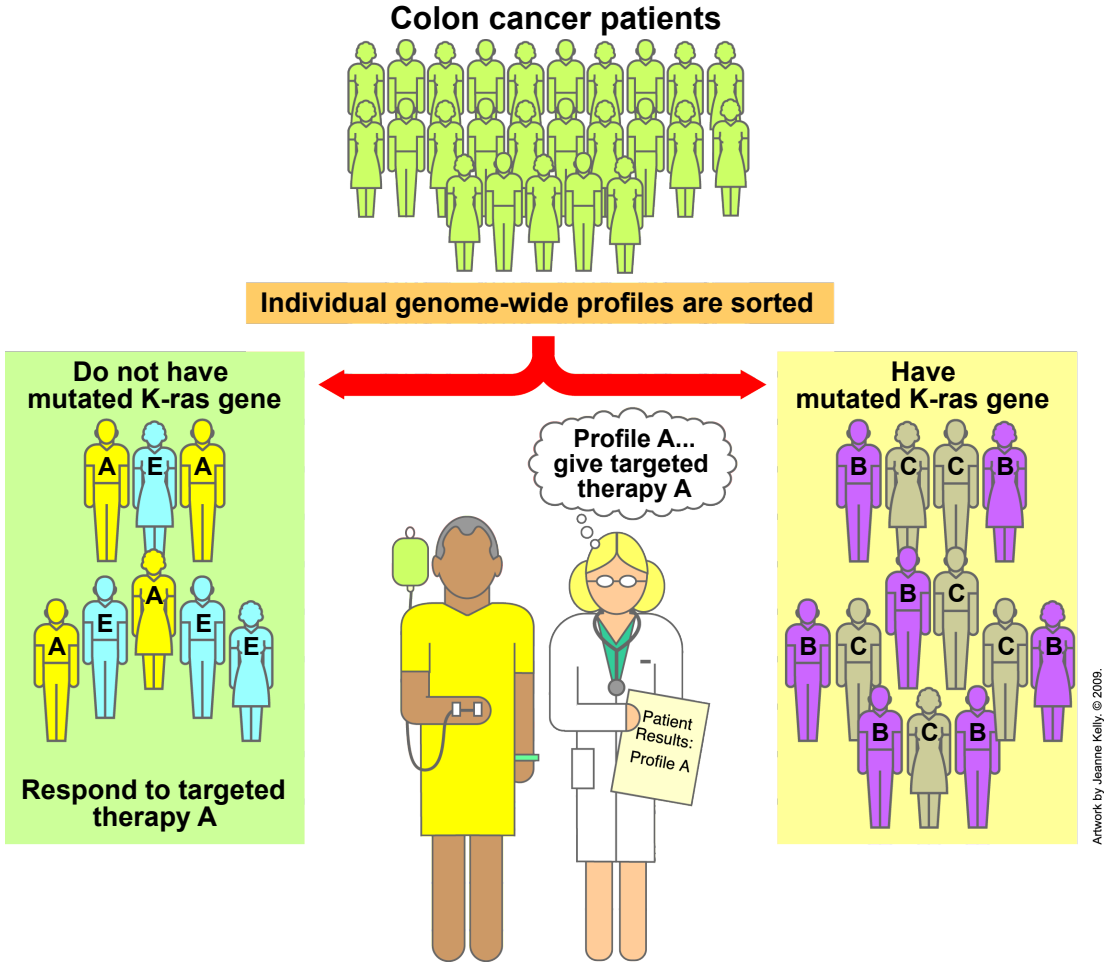
While use of genomic profiling for cancer care is still in the research phase, it is already improving diagnosis for some cancers.

# Can Genome-Wide Profiles Inform Cancer Prognosis?



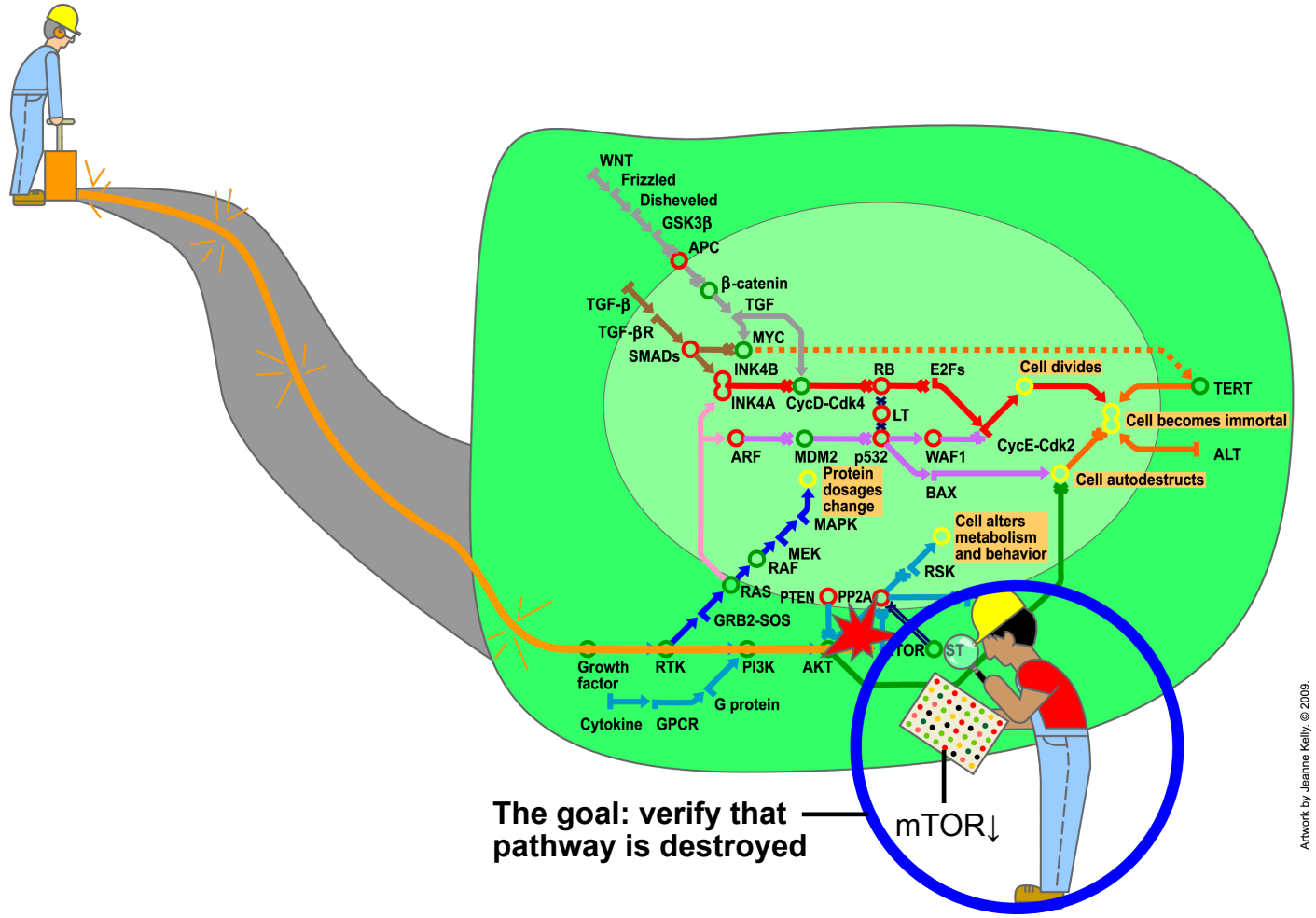

Yes. Certain gene changes have already been associated with cancer prognosis. For breast cancer, researchers have identified a set of 21 cancer-related genes whose expression is associated with risk of breast cancer recurrence among women with estrogen receptor-positive breast cancer treated surgically. The profile yields a "score" that predicts the likelihood of disease recurrence. It is not yet clear how each of the genes functions, whether separately or together, whether as "driver" or "passenger," in the pathophysiology of breast cancer.

# Can Genome-Wide Profiles Inform Cancer Treatment Planning?



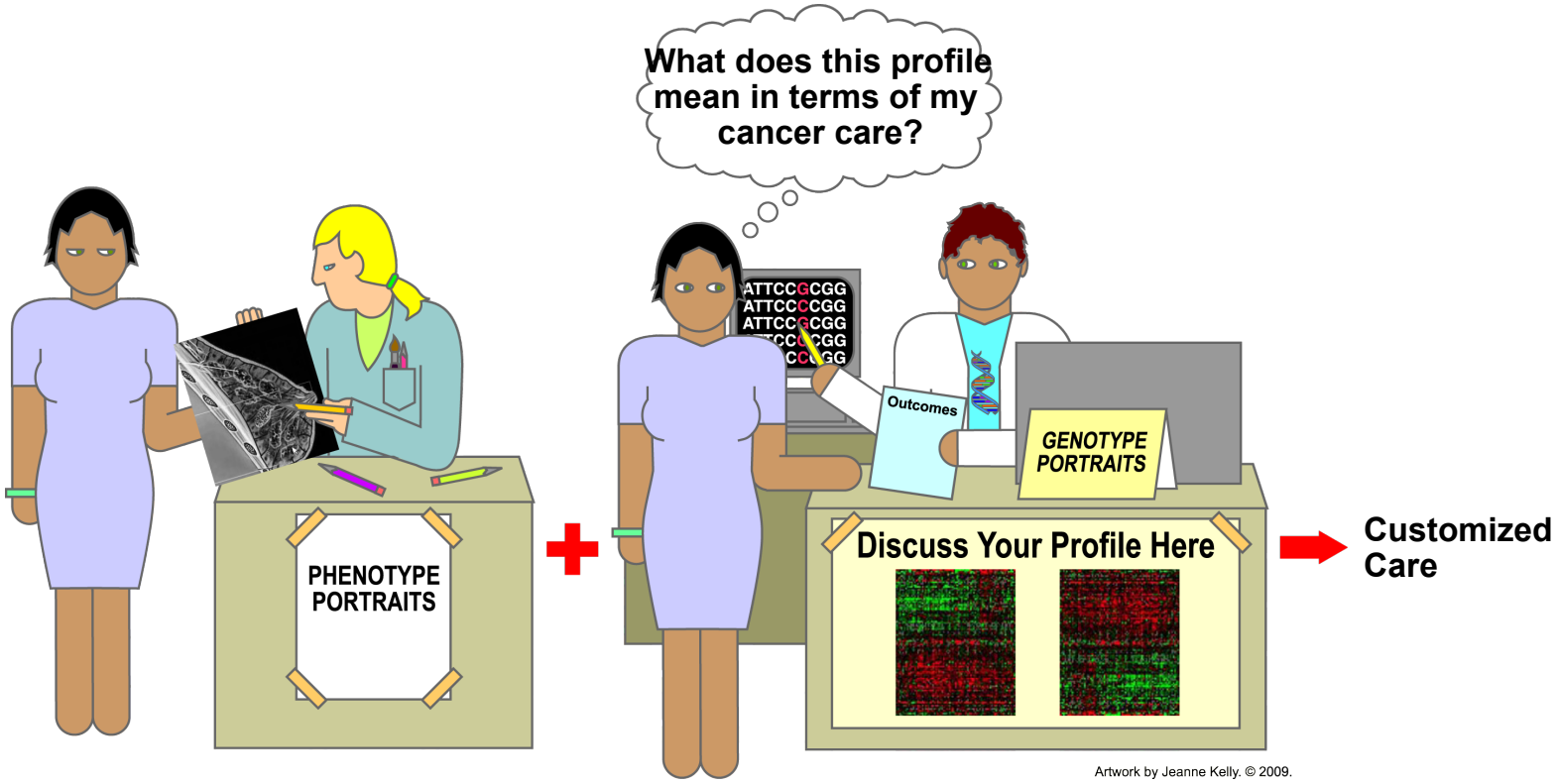

Yes, although most attempts to do this are occurring within clinical trials. If therapies are available that target genes, proteins, or pathways that appear, on the basis of genome-wide profiling, to be altered in tumors, these can be used to try to treat the patient. Researchers and clinicians are also analyzing large genomic profile databases to help match patients to the best possible treatments. The genomic profile of a newly diagnosed patient is compared with previous patients' genomic profiles, which are linked to information about how these patients were treated and responded to their treatment. This approach will allow newly diagnosed patients to be given treatments that were effective against cancers with similar genetic profiles.

# Can Genome-Wide Profiles Monitor the Response to Cancer Treatment?




Not yet. Once a molecular pathway and its activities that support a cancer are known, genomic analysis may eventually be used to monitor whether or not a pathway-specific targeted treatment has effectively disrupted this pathway, but this has not yet been demonstrated in the clinic.

# Will Genomically Informed Cancer Care Be Better for Patients?




Yes. Genome-wide profiling—whether it involves comparative genomic hybridization, karyotyping, polymorphism analysis, or gene expression profiling—is an essential element of genomically informed cancer care. The goal of genome-based care is to tailor cancer risk assessment, diagnosis, prognosis, and treatment to each individual and malignancy. Researchers are using genome-wide profiling to lay groundwork that should enable this to become a reality. However, there is still much work to be done before this new approach can be translated into better care for patients.